UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,827	01/15/2004	Michael R. Rosen	13533/48003	5518

26646 7590 11/02/2007

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
11/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,827	ROSEN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,49,51,56,57,59,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 49, 51, 56-57, 59, 66-66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims and specification filed August 16, 2007 has been received and entered. Applicants have amended claims 20, 49, 51, 56-57, 66-66 and 67, while claims 1-19, 21-48, 50, 52-55, 58 and 60-64 have been canceled. Applicants have also added claims 65-67 that are generally directed to elected invention.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group were found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 56-57, 59, 66-66 and 67 are under consideration in the instant application.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 51, 56-57, 59 and 65-67 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a method of inducing a pacemaker current in a mammal's heart, said method comprising, site specifically introducing the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is introduced by injection into the heart or cardiac catheterization; such that said composition forms a gap junction with the cells of the heart; thereby inducing a pacemaker current in the cells of the heart,

(ii) a method of expressing a functional HCN2 ion channel in the mammalian heart, said method comprising, site specifically introducing the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is introduced by injection into the heart or cardiac catheterization; such that said composition forms gap junction with the cells of the heart; thereby expressing the functional ion channel in the mammalian heart,

does not reasonably provide enablement for a method for treating any cardiac rhythm disorder or any method of increasing any pacemaker current in the heart or a method of expressing any other ion channel in any other syncytial structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's argument with respect to delivering composition of the invention to any syncytial structure is moot in view of Applicant's amendments to claims that sufficiently addresses the ground of rejection to the extent it is limiting syncytial structure to a mammalian heart. Therefore, instant amendments will overcome this ground of rejection.

Applicant's arguments filed on 8/16/2007 with respect to delivering MSC directly into the heart a composition capable of forming gap junction and those skilled in the art would consider applicants canine model and working example to

provide a reasonable correlation to the breadth of the claim Applicants also argue and cite further, Applicants direct the the publication of Plotnikov et al. (2005) *Circulation* 112: II-126 (henceforth "Plotnikov;" submitted as Exhibit A in the March 7, 2006 Amendment), which describes the injection of mHCN2-transfected hMSCs directly into left ventricular (LV) subepicardium of non-immunosuppressed adult dogs. Plotnikov reports that nests of hMSCs were found adjacent to the injection site but not at a distance. Applicants assert that Plotnikov reference describes the results of experiments conducted in accordance with methods disclosed in the specification (see page 8 and 9 of the arguments). Applicants' argument has been fully considered but they are not fully persuasive.

Specifically, Examiner has previously provided evidence to support that treating a cardiac rhythm disorder or increasing the pacemaker current in mammalian heart especially humans is complex and is considered unpredictable. Gepstein et al (Expert Opinion Biol Ther, 5(12); 1531-1537, 2005 art of record), emphasized that an optimal biological pacemaker should function continuously throughout the entire life of the treated individual and should be fail-proof, as even a short pause in its function may result in a potentially life-threatening outcome. In addition, it should provide a physiological heart rate, which may change based on the metabolic needs of the individual, ideally by reacting to changes in the neurohumoral status. Examiner would agree that specification provided guidance with respect to directly injecting hMSC transfected with nucleic acid encoding HCN2 polypeptide into anterior left ventricular wall of canine heart resulted in expression of HCN2 channel and generation of pacemaker rhythm in the canine heart. However, exemplified method does not provide any nexus between direct anterior left ventricular wall injection of composition to delivering composition directly into heart by any mean (topical, catheter) in order to create a stable physiologic rhythm and without any inflammation. In addition, neither the specification nor prior art provide any correlation of direct delivery of the

composition to anterior left ventricular wall with delivery via any mean to any other part of heart such as atrium, or Purkinje system, which would show induction in current in same manner as exemplified in the specification and would be capable of treating cardiac rhythm disorder such that sinus nodes can be returned to normal function. Furthermore, contrary to applicants' argument this is further supported by a recent report Bartune et al (Am J Physiol Heart Circ Physiol 292: H1095-H1104, 2007) that indicates that the major limitation of any cell transplantation techniques in heart is cell loss after injection. Gepstein states [f]or cell therapy approaches determining the optimal way for the delivery of the cell controlling their survival following transplantation, assuring appropriate integration of the cells with the host tissue and developing means to control the required effect all important obstacle for the future use of these strategies. The specification does not provide any guidance with respect to delivering the composition of the invention via topical application to the cell would result in physiologic rhythm without any inflammation. In fact, while reviewing the potential use of stem cells as biological pacemaker, Gepstein indicates potential of using instantly disclosed strategy that may also have a number of potential limitations. One limitation relates to the possible differentiation of the MSCs within the heart into unwanted cell lineages, such as bone and cartilage. In addition, issues relating to the long-term control of the level of transgene expression within the grafted cells, the number and distribution of the surviving grafted cell within the heart, and the degree of coupling between host and donor cells may have important consequences to the function of these cells. As a delicate equilibrium between the passive and active electro- physiological properties of the grafted and host cells, as well as the degree of coupling between these cell types, control the pacemaking function of this unit, it is possible that changes in these properties may alter this pacemaking activity. Gepstein also describe that although I_r plays a crucial role in the function of the SA nodal cells, the pacemaking function of these cells is usually the result of a

combination of the activity of a number of ionic currents. Thus, over expression of the HCN current alone will not fully recapitulate all the properties of the SA node cells. This is further supported by Xu et al (Circulation. 112(6):e82, 2005) who states" that "electrophysiological properties of hMSCs are also somewhat heterogeneous. It is uncertain over time whether hMSCs after transplantation will further differentiate into cardiac or even non-cardiac cells with electrical properties different from those of pre-transplanted cells (see page 82, col. 2, last para.). Examiner would concede that instant specification and Plotnikov provided adequate guidance for a method of inducing pacemaker current in mammalian heart, however, disclosure of investigation of cells that undergo apoptosis or number of cells that get engrafted or dose response relationship or rejection pattern of cells by delivering the composition of the invention intended for treating any cardiac rhythm disorder or increasing pacemaker current cannot be supportive of the instant specification at the time of filing of this application. As of the effective filing date of the claimed invention, the art of treating cardiac rhythmic disorder by delivering genetically modified hMSC directly into heart was unpredictable and at best evolving at the time of filing known to be. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence in the specification which supports that the exemplified canine model disclosed in the specification by applicant could be readily extrapolated to any mammalian heart for therapeutic purpose without undue experimentation. The method exemplified demonstrating induction of pacemaker current after vagal stimulation in canine model is not sufficient enablement for applicant's broadly

claimed invention of treating cardiac rhythm disorder. Thus, given that vagal stimulation in dogs does not represent a cardiac rhythm disorder in a mammal, the specification fails to provide sufficient guidance, with regard to the breadth of the claims. Accordingly, as the specification provides insufficient guidance and "experiments in biological cardiac pacing produce, at best, unpredictable results" (Ex parte Forman, 230 USPQ 546 (BPAI 1986)), therefore considering the state of the art and amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to practice the invention commensurate with full scope of the claims and rejection is maintained for reasons of record as set forth above.

On page 9 and 10, applicants argue that safety issue raised by the Examiner fall within the province of the Food and Drug Administration and not USPTO. In response, it is it is emphasized that Examiner had no intention to raise any toxicity or safety issue arising from cell transplantation as stated in previous office action. The discussion is merely intended to address problems that are associated with stem cell therapy and observed by many different investigators (see art of records). The issue is particularly important with respect to treating cardiac arrhythmic disorder, since an arrhythmic episode after cell therapy would be detrimental and defeat the purpose of any therapeutic benefit of hMSC in the treatment of any cardiac disorder. The amended claims now recite undifferentiated adult MSC, however, problem of potential differentiation to cell of other linage still exists as discussed before (supra), which would be critical for maintaining any stable physiologic rhythm.

New-Claim Rejections-Necessitated by amendments - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claims 20 and 65 recite term "capable of" in terms of forming gap junction with the cells. This term is unclear to the extent "capable of forming gap junction" is a latent property and it is unclear whether gap junction is actually formed or that it could potentially form gap junction upon modification or under certain conditions. "Capable of" implies a latent property and the conditions for the latent property must be clearly defined. The claims fail to set forth any specific structural or functional limitation that provides this property. Therefore, it is unclear if the latent property is ever obtained. Appropriate correction is required.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 49, 57 and 65-67 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al (US patent application 20040087528, dated 5/6/2004, effective filing 4/24/2002); Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005).

Levy et al describe reverse gene therapy wherein a gene therapy vector encoding a gene product is expressed in cells of an abnormal tissue of an animal to alleviate the disease (see abstract). It is noted that Levy et al also teach compositions and a method for providing progenitor cells including MSC, comprising a disease-related polynucleotide, such that cells express the polynucleotide upon administering an effective amount of cells comprising polynucleotide at the diseased site (See para 27, 31 and 109 and of the published application). Levy et al also teach delivery of transformed cells to the diseased site by localized infusion or by direct injection of a suspension of transformed cells (see para. 72 of the published application). Although, Levy et al do not teach administering a composition of MSC comprising HCN2 but he generally embraced the idea of delivering genetically modified MSC comprising therapeutic (e.g. ion channel mutation) for the treatment of cardiac disorders.

Marban et al discloses a composition of modified cells and a method comprising administration of genetically modified composition to induce or modulate pacemaker activity in a subject. It is noted that source of modified cells are cardiac myocardial cells generated from differentiated stem cells, such as embryonic bone marrow cells. The stem-cell-derived cardiomyocytes exhibiting pacemaker function then may be implanted such as by catheter or injection to targeted cardiac tissue (page10, paragraph 121 and paragraph 26). Marban also teach genes that could be used to affect cardiac firing rate includes ion channels including HCN channels (page 6, paragraph 64). The teaching of Marban et al encompasses HCN2 channel as different isoform of HCN channel were known in the art and Marban et al intend to use different HCN channels to affect firing rate of heart. However, Marban et al do not teach using a composition comprising MSC comprising HCN2.

Jansen et al teach a process comprising providing mammalian cells that express a hyperpolarization-activated cation channel including HCN2 and determining the membrane potential of the cells (col. 5, lines 5-25, col. 5, lines 60-63 and claims 1, 21 and 31. However, Jansen et al do not explicitly teach a composition of MSC comprising HCN2.

Wang et al teach administration of MSC in the heart shows growth potential in a myocardial environment and indicated the formation of gap junctions suggesting that cells derived from marrow stromal cells, as well as native cardiomyocytes, are connected by intercalated disks (see abstract and Figure 6). However, Wang et al do not teach composition-comprising MSC compromising HCN2.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the MSC cells taught by Levy et al to include other ion channels such as HCN2 taught by Marban et al, for using MSC as delivery vehicle to express HCN2 in mammalian heart for pacemaker activity. Marban and Jansen provided motivation to transfect cells with HCN channels gene as, it was generally known to

one of ordinary skill in the art that HCN2 could be used to affect cardiac firing rate. It would have been prima facie obvious to one of ordinary skill in the art to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. In addition, one of ordinary skill in the art would be further motivated to make such a modification particularly since Wang taught hMSCs engrafts in the myocardium and forms gap junction with recipient cells (supra).

One who would practice the invention would have reasonable expectation of successfully practicing the method and composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed in different cardiac or stem cell for pacemaker activity. Furthermore, Levy generally embraced the idea of using directly injecting MSC for delivering polynucleotide for the treatment of cardiac disorder, while Wang disclosed that implanted MSC form gap junction in myocardium environment. In addition, Marban taught that cardiac pacing, and subsequent heart rate, could be effectively induced by over expression of nucleotide gated (HCN) gene expression (see Marban et al, para. 20 of the published application). One of ordinary skill in art would have been motivated to combine the teaching of Levy, Marban, Jansen and Wang, because a direct administration of the composition comprising mesenchymal stem cell comprising nucleic acid encoding HCN2 into the heart by injection would have led to the engraftment of MSC with recipient heart cells resulting in expression of HCN2 and thereby induction in pacemaker current at the delivery site.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 20 and 65 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005) and Ruhparwar et al (Eur J Cardiothorac Surg. 2002; 21(5): 853-7, IDS),

The combined teaching of Marban et al, Jansen et al and Wang et al is same as presented before and relied in same manner here.

Prior to instant invention, Ruhparwar et al teach a method comprising administering cardiomyocytes (2×10^6) directly into the free wall of the left ventricle of adult canine X-linked muscular dystrophy dogs that fail to express Dystrophin in cardiac muscle. It is noted that Ruhparwar et al teach that transplanted cells are

identified by integration in the recipient heart. The expression of Connexin 43 between donor and recipient cells suggested formation of gap junctions between injected and host cardiomyocytes (see page 855, col. 1, para. 1). After catheter ablation of the AV-node, a ventricular escape rhythm emerged driving the pace of the heart and originating from the labeled transplantation site. Thus, teaching of Ruhparwar et al shows electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium in-vivo (see abstract). It is noted that Ruhparwar et al emphasizes that cardiomyocytes engraftment could initiate further research aiming at generation of autologous cardiomyocytes preferably from pluripotent embryonic or adult stem cells or by achieving controlled proliferation of adult cardiomyocytes (see page 857, col. 1, last paragraph). However, Ruhparwar et al do not teach a composition comprising MSC comprising HCN2 or method of using such composition.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the cells taught by Marban et al by expressing a nucleic acid encoding specific HCN isoforms for expressing ion channel genes in stem cell at sufficient level for pacemaker activity. Marban provided motivation to transfect cells with HCN channels gene as, it could be used to affect cardiac firing rate. One of ordinary skill in the art would be motivated to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. In addition, one of ordinary skill in the art would be motivated to modify the cardiomyocytes/embryonic bone marrow cell comprising HCN2 channel gene with MSC cells disclosed by Wang et al. particularly since Wang taught that hMSCs could engrafts in the myocardium and form gap junctions after implantation in a myocardial environment (supra). Ruhparwar et al taught electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium *in-vivo.*

One who would practice the invention would have reasonable expectation of successfully producing a composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion channel isoform could be expressed in different cardiac or stem cell for pacemaker activity. Furthermore, Wang taught that MSC engrafts and for gap junction in myocardium, while Ruhparwar et al showed the formation of gap junction between the donor and recipient cells resulting in electrical and mechanical coupling. One of ordinary skill in art would have been motivated to combine the teaching of Marban, Jansen, Wang and Ruhparwar et al because administration of the composition comprising mesenchymal stem cell comprising HCN2 would have resulted in engraftment and formation of gap junction between the MSC/differentiated cardiomyocytes with recipient heart cells to for form ion channel.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to Arguments

Levy et al, Marban et al, Jansen and Wang et al

Applicant's arguments filed on August 16, 2007 have been fully considered but they are not fully persuasive. As an initial matter it is noted that instant rejection is made to the breadth of the claims that reads on claimed composition and method intended to induce pacemaker current or express ion channel.

Applicants in their argument point out that Applicants have amended the claims to recite the site-specific introduction of a HCN2- expressing MSC directly into a mammalian heart and that the introduced MSC are capable of forming gap junctions with the cells of the heart. Applicants maintain that the cited references do not, alone or in combination, disclose or suggest the subject matter encompassed by the claims as amended. Applicants then describe in length the reverse gene therapy method of Levy and asserts that the expression of mutant HERG protein can be used to treat patients afflicted with re-entrant atrial flutter but fails to teach the expression of HCN2.

In response, it is noted that if Levy had taught a method to express HCN2 with disclosed method then this would have been an anticipation rejection and not obviousness type rejection.

Claim interpretation: With respect to amendments to the claims drawn to composition of the invention capable of forming a gap junction with cell, it is noted that recitation of capable is a latent property and it is not apparent whether this property is ever achieved (also see enablement rejection). In addition, all the method claims require site-specific administration of the composition directly into the mammal's heart.

It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention of MSC comprising HCN2. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It also appears that applicant is attempting to attack each reference individually. However, in a 103 rejection the references must be considered as a whole. In the instant case, contrary to applicant's argument Levy et al teach a method that uses hMSCs that could be transformed so as to contain a gene of interest (See para. 58 of the specification). It would be obvious for one of ordinary skill in the art at the time of invention to transform hMSC taught by Levy et al to deliver gene at the intended target site. Marban and Jansen provided guidance with respect to transfect cells with HCN channels gene as, it was generally known to one of ordinary skill in the art that HCN2 could be used to affect cardiac firing rate. It would have been prima facie obvious to one of ordinary skill in the art to use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential and Marban had disclosed the usefulness of HCN channel gene in pacemaker activity. In addition, it was also generally known at the time of filing to one of ordinary skill in the art that hMSCs engrafts in the myocardium and forms gap junction with recipient cells as evidenced by the teaching of Wang et al. It would have been obvious to one of ordinary skill in the art to modify the composition of Levy to modify the composition of MSC by transforming with HCN2 with predictable result, particularly since art had already shown that HCN2 and other ion channel isoform could be expressed in different cardiac or stem cell for pacemaker activity. Furthermore, Levy generally embraced the idea of using

directly injecting MSC for delivering polynucleotide, while Wang disclosed that implanted MSC form gap junction in myocardium environment. It is noted that direct administration of the composition comprising mesenchymal stem cell comprising nucleic acid encoding HCN2 into the heart by injection would have led to the engraftment of MSC with recipient heart cells resulting in expression of HCN2 and thereby induction in pacemaker current which would be implicit in the teaching.

Marban, Jansen, Wang and Ruhparwar

Applicants argue that Marban, Jansen, or Wang disclose, or suggest, a composition comprising MSCs incorporated with a nucleic acid encoding HCN2, wherein the MSC is capable of forming a gap junction with a cell of a mammalian heart in the absence of differentiation of the MSC. Applicants assert that, in teaching the administration of differentiated cardiomyocytes into the heart, Ruhparwar does not remedy the deficiencies of Marban, Jansen, and Wang in this regard.

In response, as stated before recitation of capable in the claim is a latent property and it is not apparent whether this property is ever achieved (also see enablement rejection). Furthermore, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. In the instant case, direct injection of genetically modified multipotent stem cells into heart of a mammal for inducing pacemaker current was known in prior art. and engraftment and formation of gap junction of hMSCs in the myocardium and with recipient cells Furthermore, Marban et al provided guidance with respect to delivery of

transformed multipotsnet stem cells directly into heart by injection for inducing current. It would have been obvious to one of ordinary skill in the art to try to use hMSC with predictable results particularly since Wang taught that hMSCs could engrafts in the myocardium and form gap junctions after implantation in a myocardial environment, while Ruhparwar et al showed the formation of gap junction between the donor and recipient cells resulting in electrical and mechanical coupling. One of ordinary skill in art would have been motivated to combine the teaching of Marban, Jansen, Wang and Ruhparwar et al because administration of the composition comprising mesenchymal stem cell comprising HCN2 would have resulted in engraftment and formation of gap junction between the MSC/differentiated cardiomyocytes with recipient heart cells to for form ion channel with reasonable expectation of success.

Maintained -Double Patenting

Claims 20, 49, 51, 56-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20-59 of copending Application no 10/342506 (US Patent Publication no 20040137621). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and a method of inducing current and a method of treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. As indicated by applicants a Terminal disclaimer later would obviate this rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least

one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

/Thaian N. Ton/
Primary Examiner
Art Unit 1632